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The Office Action alleges that the application is directed to two distinct and independent inventions. Provided below are the two inventions set forth in the Office Action.

Group I: claims 1-18, directed to LM609 grafted antibodies and encoding nucleic acids;

Group II: claims 19-25, directed to methods of inhibiting the function of $\alpha_v\beta_3$ and of treating an $\alpha_v\beta_3$ -mediated disease.

Election of one of the inventions is required under 35 U.S.C. § 121. Although the restriction requirement is traversed for the reasons discussed below, Applicants elect the claims set forth in Group I, claims 1-18, for examination.

Applicants traverse the restriction requirement with respect to the claims of Groups I and II. Applicants submit that examination of the claims of Groups I and II together would not present an undue burden upon the Examiner. Specifically, examination of the claims of Group I is directed to a search of LM609 grafted antibodies, particularly the LM609 grafted antibody sequences. Similarly, the claims of Group II also require a search of LM609 grafted antibodies since the methods recite the use of these antibodies. A search of the claims of Group I will necessarily encompass the subject matter claimed in Group II. Therefore, division of the claims into two groups would result in duplicative searches and a waste of PTO resources. In light of these remarks, Applicants respectfully request the Examiner reconsider the restriction requirement with regard to Groups I and II and examine the claims of these groups together.

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Claims 1-18 stand provisionally rejected under the judicially created doctrine of obviousness type double patenting as allegedly unpatentable over claims 1-48 of copending application serial number 08/791,391. Applicants respectfully request that this provisional ground of rejection be deferred until there is an indication of allowable subject matter.

The present invention provides LM609 grafted antibodies exhibiting selective binding affinity to $\alpha_v\beta_3$. The antibodies are non-mouse antibodies or functional fragments thereof that contain heavy and light chain CDR amino acid sequences derived from LM609. Nucleic acids encoding LM609 grafted heavy and light chains are additionally provided. Applicants have reviewed the Office Action and respectfully traverse all grounds for rejecting the claims for the reasons that follow.

REJECTIONS UNDER 35 U.S.C. § 112

Claims 1-18 stand rejected under 35 U.S.C. § 112, first and second paragraphs, as allegedly lacking enablement and as allegedly failing to particularly point out and distinctly claim the subject matter of the invention. Applicants will respond in turn to each of the rejections as they pertain to the referenced claims.

Claims 1-18 stand rejected under 35 U.S.C. § 112, first and second paragraphs, as allegedly unclear because the characteristics of the terms "substantially the same" and "functional fragment thereof" are not known. The Office Action states that many different amino acid and nucleic acid sequences as well as many different forms and modifications are encompassed by these terms. The Office Action further asserts that it is

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unclear which particular "sameness" or "function" are being referred to as it relates to the structure and/or function of LM609 grafted antibodies and nucleic acids encoding LM609 grafted antibodies. The Office Action also states that the metes and bounds of "substantially the same" and "functional fragment thereof" have not been defined in the specification.

The Office Action additionally alleges that undue experimentation would be required to produce and investigate all possible recombinant antibodies and nucleic acids without more explicit guidance from the disclosure. In this regard, the claims are alleged to broadly encompass an extremely large number of recombinant antibodies and nucleic acids encoding the recombinant antibodies and broadly encompass a significant number of inoperative species. The Office Action states that the criticality or permissibility of the modifications encompassed by the claims that result in "substantially the same" and "functional fragment thereof" that provide LM609 grafted antibodies and nucleic acids encoding the amino acids has not been clearly shown or defined and is meaningless in the absence of a mathematical algorithm and in the absence of reciting a function.

Applicants submit that the terms "substantially the same" and "functional fragment thereof" are clear to one skilled in the art in view of the specification. The specification teaches that a nucleotide or amino acid sequence that is "substantially the same" shows a considerable degree, amount or extent of sequence identity when compared to a reference sequence (page 12, line 18, to page 13, line 16). A nucleotide or amino acid sequence which is substantially the same as a heavy or light chain of a LM609 grafted antibody is a sequence which exhibits

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characteristics that are recognizable as encoding or being the amino acid sequence of a LM609 grafted antibody, including minor modifications. Therefore, Applicants submit that the meaning of the term "substantially the same" is clear and definite.

The specification further teaches that a "functional fragment" of a LM609 grafted antibody is a portion of a LM609 grafted antibody, including heavy or light chain polypeptides, which still retains some or all of the $\alpha_v\beta_3$ binding activity, $\alpha_v\beta_3$ binding specificity and/or integrin $\alpha_v\beta_3$ -inhibitory activity (page 14, lines 4-23). The specification also teaches that the functional fragments include, for example, antibody functional fragments such as Fab, F(ab)₂, Fv and single chain Fv (scFv). Although Applicants submit that the term "functional fragment" is clear in view of the specification, claim 1 has been amended to indicate that the LM609 grafted antibody exhibits selective binding affinity to $\alpha_v\beta_3$. Therefore, Applicants submit that the meaning of the terms "substantially the same" and "functional fragment thereof" are clear and definite.

In regard to the alleged requirement of undue experimentation to produce a large number of recombinant antibodies, Applicants submit that the specification provides sufficient description and guidance so as to enable those skilled in the art to practice the invention as claimed. The invention is directed to LM609 grafted antibodies and is limited to those LM609 grafted antibodies exhibiting selective binding affinity to $\alpha_v\beta_3$. Thus, the claims do not encompass an extremely large number of recombinant antibodies, including a significant number of inoperative species as asserted in the Office Action. Rather, the claims encompass only those antibodies exhibiting selective binding affinity to $\alpha_v\beta_3$.

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Applicants further submit that the specification clearly defines the modifications encompassed by the terms "substantially the same" and "functional fragment thereof" in regard to LM609 grafted antibodies. The specification teaches that minor modifications of the nucleotide sequences are included as heavy and light chain LM609 grafted antibody encoding nucleic acids and their functional fragments (page 17, line 21, to page 18, line 11). Minor modifications include changes in nucleotide sequence that do not change the encoded amino acid sequence due to degeneracy in the genetic code and changes that result in conservative amino acid substitutions.

Minor modifications resulting in substantially the same sequence also include changes that allow for the functional replacement of amino acids by identifying the amino acids that are desired to be changed, incorporating the changes into the encoding nucleic acid and then determining the function of the recombinantly expressed and modified LM609 grafted antibody polypeptide (page 18, line 24, to page 19, line 16). The specification also teaches methods of screening for $\alpha_v\beta_3$ binding activity (see Example I). Therefore, an amino acid sequence or nucleic acid encoding the amino acid sequence that incorporates minor modifications is "substantially the same" if it exhibits characteristics that are recognizable as representing the sequence of a LM609 grafted antibody, including $\alpha_v\beta_3$ binding activity, $\alpha_v\beta_3$ binding specificity and integrin $\alpha_v\beta_3$ inhibitory activity (page 13, lines 1-16 and page 14, lines 4-10). Thus, knowledge of the contribution of particular amino acid residues in CDRs and framework regions to successful humanization of functional antibodies is not required since the claims are limited to only those LM609 grafted antibodies exhibiting selective binding affinity to $\alpha_v\beta_3$ and since the specification

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teaches the LM609 grafted antibody sequences as well as how to screen for $\alpha_v\beta_3$ binding activity.

In regard to the alleged requirement of a mathematical algorithm to provide meaning to the term "substantially the same," Applicants submit that the specification provides sufficient description and guidance to enable one skilled in the art to practice the invention as claimed. The claimed invention encompasses only those LM609 grafted antibodies having substantially the same heavy and light chain CDR amino acid sequences as found in LM609 and exhibiting $\alpha_v\beta_3$ binding specificity but is not dependent on a particular percentage of sequence identity as defined by a mathematical algorithm. Therefore, a mathematical algorithm allowing input of parameters for sequence comparison to define a particular percentage of sequence identity is unnecessary in regard to determining whether an amino acid or encoding nucleic acid sequence is substantially the same because the claims recite both the LM609 grafted antibody sequence and a binding function. Once the sequence becomes sufficiently divergent that binding specificity to $\alpha_v\beta_3$ is no longer exhibited, the sequences can no longer be considered substantially the same. Thus, determination of whether a sequence is substantially the same as one encoding a LM609 grafted antibody depends on whether the sequence encodes a LM609 grafted antibody exhibiting selective binding activity to $\alpha_v\beta_3$.

In light of the above remarks, Applicants submit that the amendment of the claims to LM609 grafted antibodies exhibiting selective binding affinity to $\alpha_v\beta_3$, together with the teachings of the specification, provide sufficient guidance to enable one skilled in the art to practice the invention as claimed without undue experimentation. Thus, Applicants submit

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that the specification clearly defines the terms "substantially the same" and "functional fragments thereof". Furthermore, Applicants submit that the specification provides sufficient guidance to allow one of ordinary skill in the art to make and use LM609 grafted antibodies, or a functional fragment thereof, having substantially the same amino acid or nucleotide sequence as the LM609 grafted antibodies specifically claimed and exhibiting selective binding affinity to $\alpha_v\beta_3$. Therefore, the rejection of claims 1-18 under 35 U.S.C. § 112, first and second paragraphs, as allegedly lacking enablement and as allegedly vague and indefinite is respectfully requested to be withdrawn.

Claims 1-18 also stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement due to the requirement that the LM609 antibody be available or readily obtainable to practice the claimed invention. The Office Action states that if the antibody is not available or obtainable, the enablement requirements may be satisfied by deposit of the antibody under conditions of the Budapest Treaty. Alternatively, the Office Action states that disclosure of the sequence of an entire immunoglobulin satisfies the enablement requirement.

Applicants wish to initially draw the Examiner's attention to the fact that the LM609 antibody is not required to practice the invention as claimed. Applicants claimed invention is directed to LM609 grafted antibodies. There is no claim directed to the LM609 antibody nor is the antibody required to make and use the invention as claimed. Instead, all that is required is the LM609 variable region nucleotide sequences or the CDR encoding nucleotide sequences thereof. Applicants have provided sufficient enablement for the claimed invention by reciting these sequences in the specification.

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In this regard, the nucleotide sequences encoding the LM609 heavy and light chain variable regions are recited in Figure 2 and on page 6, lines 8-17 as SEQ ID NOS:5 and 7, respectively. Given these sequences, one skilled in the art can routinely make and use the claimed LM609 variable region nucleotide sequences using methods well known in the art. Such methods include, for example, oligonucleotide synthesis and recombinant cloning methods and are described in the specification on page 26, line 15 to page 27, line 2, and in Examples I and II.

Similarly, to obtain the claimed LM609 grafted antibodies, all that is necessary to practice the invention as claimed are the nucleotide sequences encoding the LM609 CDRs. These sequences are recited on page 6, lines 8-17 (SEQ ID NOS:5 and 7) and are defined in Table 1, page 12. These LM609 CDR sequences are also recited in context with their acceptor variable region framework sequences on page 23, Table 2, and page 30, Table 4, for LM609 grafted antibody and LM609 encoding sequences, respectively. Given these sequences, one skilled in the art can routinely graft these CDRs into an acceptor variable region framework to produce the claimed LM609 grafted antibody encoding nucleotide sequences of the invention. Nevertheless, Applicants have recited the entire nucleotide sequence of the above LM609 heavy and light chain variable regions as SEQ ID NOS:1 and 3, respectively. Therefore, one skilled in the art can make and use the claimed nucleotide sequences by routine methods known in the art. Once produced, the nucleotide sequences can be expressed to generate the claimed LM609 grafted antibodies of the invention. Thus, the disclosure of the nucleotide sequence of the LM609 heavy and light chain variable regions and the CDR sequences therein is all that is necessary to practice the

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invention as claimed. Therefore, the rejection of claims 1-18 as allegedly lacking enablement is respectfully requested to be withdrawn.

Claims 1-18 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite because the characteristics of "LM609" are unknown. The Office Action alleges that "LM609" is merely a laboratory designation that does not clearly define the claimed product.

Applicants submit that the term "LM609" is clear and definite as it is used to refer to the claimed grafted antibodies. The term is used to refer to the donor antibody from which the CDRs of the grafted antibody are derived. The specification teaches on page 7, line 24, to page 8, line 2, that "LM609" is a murine monoclonal antibody specific for the integrin $\alpha_v\beta_3$, described by Cheresh, Proc. Natl. Acad. Sci. USA 84:6471-6475 (1987) and Cheresh and Spiro, J. Biol. Chem. 262:17703-17711 (1987). The specification further teaches on page 8, lines 15-22, that the LM609 grafted antibodies of the invention are non-mouse antibodies containing substantially the same heavy and light chain CDR amino acid sequences as found in LM609 and absent the substitution of LM609 amino acid residues outside of the CDRs as defined by Kabat et al. Nevertheless, it is irrelevant whether or not the term LM609 is a laboratory designation since the claims recite descriptive and distinguishing characteristics of the grafted antibodies.

The LM609 grafted antibodies, as claimed, are directed to substantially the same heavy and light chain variable region amino acid sequences as that shown in SEQ ID NOS:2 and 4, respectively. The claimed sequences contain the LM609 CDRs as

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taught in the specification. Moreover, the claimed LM609 grafted antibodies of the invention are also characterized as exhibiting selective binding affinity to $\alpha_v\beta_3$. Thus, regardless of whether the term "LM609" is a laboratory designation, the grafted antibodies as claimed recite both structural and functional characteristics of the antibodies. Applicants therefore maintain that the meaning of the term "LM609" is clear and respectfully request this ground of rejection be removed.

Claims 1-18 also stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite because the term "grafted" is allegedly unclear. The Office Action states that "grafted" antibodies encompass any number of recombinant forms of antibodies and that sufficient direction to define the grafted forms has not been provided.

Applicants submit that the term "grafted" is clear and definite when read in light of the specification. Applicants have set forth the meaning of the term on page 9, lines 17-24, where a "grafted antibody" is described as having substantially the same heavy or light chain CDRs of a donor antibody and absent of the substitution of donor amino acid residues outside of the CDRs as defined by Kabat et al. The CDRs of LM609 are described on page 6, lines 8-17, and are defined in Table 1, page 12, Tables 2 and 3, pages 23-24, and Tables 4 and 5, page 30, for both the nucleotide and amino acid sequences. Given these teachings, one skilled in the art can make and use a LM609 grafted antibody as claimed. Furthermore, specific heavy and light chain variable region sequences are recited and the $\alpha_v\beta_3$ binding activity is recited in the claims directed to the LM609 grafted antibody.

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Moreover, "grafted" is an art recognized term which refers to the functional replacement of antibody CDRs and which is the subject matter of U.S. Patent No. 5,225,539. The specification teaches on page 8, lines 15-22, that LM609 grafted antibodies are grafted antibodies produced by the functional replacement of CDRs derived from the LM609 antibody. The methods used followed those described in U.S. Patent No. 5,225,539 and in "Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man" (see specification, page 15, lines 4-20).

Finally, the specification teaches how to make and test for LM609 grafted antibodies. For example, the specification teaches on page 16, lines 7-21, that LM609 grafted antibodies were generated by substituting nucleic acids encoding heavy and light chain CDRs of LM609 into the respective human chain encoding nucleic acids. A population of CDR grafted heavy and light chain variable regions, where all possible changes outside of the CDRs were represented, was generated and screened for binding activity. The specification describes the generation of grafted antibodies and methods of screening for $\alpha_v\beta_3$ binding activity (see Example II). Thus, the specification provides sufficient guidance as to the meaning of the term "grafted" and how to make LM609 grafted antibodies and screen for those having $\alpha_v\beta_3$ binding activity. Therefore, Applicants submit that the meaning of the term "grafted" is clear and respectfully request this rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 102

An issue of public use or on sale activity has been raised under 35 U.S.C. § 102(b). The Office Action states that

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articles in Biotechnology Newswatch, dated January 16, 1995, and February 6, 1995, disclose the use of LM609 antibody including the humanized version of the antibody. The Office Action also notes that Dr. Cheresh, who developed the LM609 antibody, is not listed as an inventor.

Applicants submit that the claimed compositions directed to LM609 grafted antibodies were not in public use or on sale in this country more than one year prior to the filing date of the above-identified application. The description within the Biotechnology Newswatch articles do not establish a *prime facie* case for public use or on sale, much less do these articles raise an issue of public use or on sale extending beyond the experimental use exception. *In re Smith*, 714 F.2d 1127, 218 USPQ 976 (Fed. Cir. 1983); *Hycor Corp. v. Schlueter Co.*, 740 F.2d 1529, 222 USPQ 553 (Fed. Cir. 1984). The cited articles are press releases describing the results obtained with the mouse monoclonal antibody and the continued development and testing of a grafted LM609 antibody. These uses do not constitute a public use or sale of a LM609 grafted antibody.

In light of the above remarks, Applicants maintain that LM609 grafted antibodies were neither in use or on sale in this country more than one year prior to the filing date of the above-identified application and respectfully request this rejection be withdrawn.

In regard to the issue of inventorship, the claimed invention is directed to LM609 grafted antibodies, which are non-mouse antibodies. Inventorship has been previously determined within the meaning of 35 U.S.C. § 101 and as interpreted by the

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courts. *Burroughs Wellcome Co. v. Barr Laboratories Inc.* 40 F.3d 1223, 32 USPQ 2d 1915 (Fed. Cir. 1994). In light of the Examiner raising this issue in the Office Action, inventorship has been reviewed and determined to be correct.

Claims 1 and 15-18 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Brooks et al., Cell 79:1157-1164 (1994). The Office Action states that Brooks et al. describe the LM609 antibody.

Applicants submit that the claimed compositions directed to LM609 grafted antibodies are novel over Brooks et al. The cited reference appears to describe the inhibition of angiogenesis by the $\alpha_v\beta_3$ inhibitory monoclonal antibody LM609. As described previously, LM609 is a mouse monoclonal antibody. In contrast, the claimed LM609 grafted antibodies are non-mouse antibodies containing substantially the same heavy and light chain CDR amino acid sequences as found in LM609 (page 8, lines 15-22, as well as SEQ ID NOS:5 and 7 and Tables 1, 2, and 4 on pages 12, 23 and 30, respectively). The claimed antibodies recite these specific CDR sequences grafted into human variable region framework sequences (SEQ ID NOS:2 and 4 for LM609 grafted antibodies). Brooks et al. do not teach the LM609 CDR region sequences nor do they teach these CDR region sequences grafted into a human antibody variable region framework as is described and claimed as SEQ ID NOS:2 and 4. The claimed antibodies and sequences thereof are distinct from the mouse monoclonal antibody LM609 described in the cited reference. Thus, Brooks et al. cannot anticipate the invention as claimed, and this ground of rejection is respectfully requested to be withdrawn.

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Claims 1 and 15-18 also stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Choi et al., J. Vascular Surg. 19:125-134 (1994). The Office Action states that Choi et al. describes the LM609 antibody.

Applicants submit that the claimed compositions directed to LM609 grafted antibodies are novel over Choi et al. The cited reference appears to describe inhibition of PDGF-mediated human smooth muscle cell migration by the anti- $\alpha_v\beta_3$ monoclonal antibody LM609. As discussed above, the claimed LM609 grafted antibodies are non-mouse antibodies having specific CDR sequences grafted into human variable region framework sequences (SEQ ID NOS:2 and 4 for LM609 grafted antibodies). Choi et al. do not teach the LM609 CDR region sequences nor do they teach these CDR region sequences grafted into a human antibody variable region framework as is described and claimed as SEQ ID NOS:2 and 4. Thus, Choi et al. cannot anticipate the invention as claimed, and this ground of rejection is respectfully requested to be withdrawn.

Claims 1 and 15-18 stand rejected under 35 U.S.C. 102(a)(e) as allegedly anticipated by Kim et al., U.S. Patent No. 5,578,704. The Office Action states that Kim et al. describe the LM609 antibody.

Applicants submit that the claimed compositions directed to LM609 grafted antibodies are novel over Kim et al. The cited reference appears to describe hybridomas and murine monoclonal antibodies that specifically bind to $\alpha_v\beta_3$ integrin on human osteoclasts. However, Kim et al. do not teach the LM609 CDR region sequences nor do they teach these CDR region sequences grafted into a human antibody variable region framework as is

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described and claimed as SEQ ID NOS:2 and 4. Thus, Kim et al. cannot anticipate the invention as claimed, and this ground of rejection is respectfully requested to be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-18 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Brooks et al., *supra*, Choi et al., *supra*, or Kim et al., *supra*, in view of the known art related to gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof. The Office Action states that Brooks et al. describe $\alpha_v\beta_3$ -specific antibodies that were important in determining signaling events critical to the survival and differentiation of vascular cells undergoing angiogenesis and that integrin $\alpha_v\beta_3$ -specific antagonists such as LM609 antibody could promote tumor regression. The Office Action also states that Choi et al. describe the important role of the $\alpha_v\beta_3$ integrin in smooth muscle cell migration *in vitro* and neointimal hyperplasia *in vivo* with $\alpha_v\beta_3$ -specific antagonists, including the LM609 antibody.

In regard to the Kim et al. reference, the Office Action states that the cited reference describes $\alpha_v\beta_3$ -specific antibodies that were expected to be valuable diagnostic and therapeutic tools in studying the biological role of $\alpha_v\beta_3$ and the structural-functional relationships with its various ligands. The Office Action states that Kim et al. also describe the generation of recombinant or humanized antibodies. The Office Action acknowledges that the cited reference does not teach the humanization of the LM609 antibody and nucleic acids encoding the

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humanized antibody but states that humanization of antibodies was obvious to one of ordinary skill in the art.

Applicants submit that the claimed compositions directed to LM609 grafted antibodies and encoding nucleic acids are unobvious over the cited references. Brooks et al. and Choi et al. describe using LM609 to inhibit $\alpha_v\beta_3$, but do not teach or suggest the nucleotide sequences encoding LM609 or the amino acid or nucleotide sequence of the claimed LM609 grafted antibodies. Kim et al. appears to discuss methods to isolate DNA encoding monoclonal antibodies. However, the cited reference does not teach or suggest the nucleotide sequences encoding LM609 or the amino acid or nucleotide sequence of the claimed LM609 grafted antibodies. Knowledge of a protein does not give a conception of a particular DNA encoding it. *In re Deuel*, 34 USPQ 2d 1210, 1214 (Fed. Cir. 1995). Since none of the cited references teach or suggest the claimed nucleotide sequences recited as SEQ ID NOS:1 and 3 or the claimed amino acid sequences recited as SEQ ID NOS:2 and 4 and containing the CDR regions derived from the encoding LM609 nucleotide sequences, Applicants maintain that Brooks et al., Choi et al. or Kim et al. cannot render the claimed invention obvious. Therefore, the rejection of claims 1-18 as allegedly obvious is respectfully requested to be withdrawn.

CONCLUSION


In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The

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Examiner is invited to call Cathryn Campbell or the undersigned agent if there are any questions.

Respectfully submitted,

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